American Journal of Pharmaceutical Education **2020; 84 (12) Article 8184.**

COMMENTARY

Harnessing Placebo Responses to Improve Health Outcomes

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Submitted May 22, 2020; accepted August 12, 2020; published December 2020.

Variations in the psychosocial aspects of the provision of health care treatments can measurably affect the health outcomes resulting from the use of such treatments. These benefits (or harms) in outcomes result from processes beyond the specific physiological mechanisms induced by the treatments. Such phenomena can be most clearly seen when physiological improvements are induced by administering inert placebo medications in the same manner as if they were actual medications. By logic, these physiological improvements should also occur during the provision of actual medications and potentiate the latter's effectiveness. There are likely many manipulations of the patient-clinician interaction that can positively or negatively affect therapeutic outcomes for many conditions. Clinicians should thus be able to make choices in their behavior that optimize any possible increases in drug effectiveness resulting from placebo responses. This commentary makes the assertion that pharmacists are ethically obligated to learn and practice techniques that maximize placebo responses and that it is incumbent upon the Academy to explore and understand such techniques and effectively teach them to students.

Keywords: placebo response, major depression, pain, affective skills

A recent report by Meltzer-Brody and colleagues regarding two successful phase 3 trials for a new pharmacological approach to treating postpartum depression has generated notice. A 60-hour inpatient infusion of brexanolone, a proprietary preparation of the neurosteroid allopregnanolone, significantly improved new mothers' ratings of their depression symptoms by the end of the infusion.[1] "Significantly" here means only that the average improvement in depression ratings of the women who received active brexanolone was statistically separated from the average rating improvement for the women who received a placebo treatment. Within hours of starting treatment, women in all arms of the studies had their Hamilton depression rating scores reduced by approximately 50% to 70% from their pretreatment scores, and the average improvements at the end of the 60-hour infusion for the women in the placebo arms were fully 72% to 82% as large as the average improvements for those taking the active drug. At 30 days posttreatment, women in all arms of the two trials had consistently maintained their improvement. Also, in the second trial, there was no statistical difference between the depression rating scores seen in patients in the active treatment and placebo treatment arms of the study, with those in the placebo arm having a nominally lower average score (ie, less depression) than those in the treatment arm. These results show that depressed perinatal women who were placed in inpatient care and monitored for a days-long infusion quickly and rather dramatically improved, even if the infusion was inert, and that the care alone provided three-fourths of the total benefit separate from any benefit resulting from drug action.

Many placebo-controlled trials of drug treatments for major depressive disorder have demonstrated similar results, where patients in the placebo arm experience improvements that are nearly as large as those seen in the active arm. Indeed, some of these trials have gone unreported because the active treatment was not significantly better than placebo even though there was significant improvement in depression scores for both arms of the study.[2] These consistent observations of large placebo responses in antidepressant trials clearly demonstrate that the process in which a patient with major depression enters a trial, has their depression regularly evaluated, and receives what everyone involved hopes is an effective treatment frequently improves the patient's mood even if the pill they swallow or the infusion they receive contains only inert substances. Somehow, purely behavioral, cognitive, and emotional processes related to receiving treatment, but outside of any exogenous chemical influence, can induce brain mechanisms that relieve the scourge of depression.

Some of the conditions and mechanisms that best induce placebo responses in depression have been

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identified and the changes in brain activity induced in placebo responses have been elucidated, showing that the frontal (cognitive and executive functions) and limbic (emotional processing) regions of the brain are involved.[3,4] The *expectancy* of patients is the degree of their belief prior to treatment that they will improve as a result of the treatment. If this expectation is experimentally manipulated when providing an antidepressant, patients with greater expectancy show greater improvements.[5] In addition, the response to both placebo and real antidepressant medications can be predicted by a measure of the quality of the therapeutic alliance, that is, the relationship between provider and patient.[6] Because pharmacists are frequently the actual providers of medications they are uniquely positioned to influence the behavioral, cognitive, and emotional processes that accompany medical treatment for depression and possibly increase the effectiveness of antidepressants.

The experience of pain can also be significantly altered, for better or worse, by behavioral, cognitive, and emotional manipulations surrounding its treatment. Relief from placebo treatments can be easily and consistently induced and typically blocked by naloxone, showing that endogenous opioids are often (but not always) involved.[7] Conversely, when a subject with pain is given a hidden dose of analgesics and is not informed that he or she is being given the drug, pain relief is significantly less than when he or she is informed and can see that the drug is being administered.[8] In fact, the difference in analgesia between hidden and open paradigms, with all other factors being the same, is a direct quantification of the placebo response and can comprise more than a twofold increase in pain reduction.[9] These results are clear indications that the information provided to patients and the nature of their experience with medical interventions can affect how well pain medications work by impacting innate, internal pain control mechanisms. Indeed, the well-studied mechanism of the descending analgesia system may explain much of the placebo responses seen in pain treatment, where higher-level cortical centers induce activity in midbrain and brainstem centers that ultimately interfere with ascending pain transmission in the dorsal horn of the spinal cord and elsewhere.

Other manipulations affect pain outcomes in different ways and reveal opportunities for clinicians to positively or negatively impact the degree to which a given treatment reduces pain. For example, previous experience can condition patients to expect either relief or a lack of relief from a treatment, depending on the outcomes of the earlier experiences, and this expectation affects the actual relief attained.[10] Furthermore, when subjects had an exaggerated memory of pain, compared to their earlier concurrent rating of the same pain experience, conditioning produced a larger placebo effect.[11] Interestingly, when conditioning was performed with a non-opioid medication such as ketorolac, the subsequent placebo effect was not blocked by naloxone, indicating that mechanisms other than the actions of endogenous opioids can be involved in placebo responses.[12] Perhaps most importantly to the role of clinicians, verbal suggestions can influence the degree of pain relief from medications. Postoperative patients who were given an initial saline injection and told it was a powerful painkiller needed a third less subsequent (real) painkiller compared to a control group of patients who were told nothing when given the initial saline injection.[13] Conversely, negative suggestions regarding the effectiveness of an analgesic medication can reduce the effectiveness of that medication, triggering what are known as *nocebo* responses.[14] Other neurotransmitter systems in addition to the opioidergic have been shown to mediate aspects of placebo responses, including dopamine in positive expectation[15] and cholecystokinin in the mediation of hyperalgesic nocebo responses.[14] A large body of brain imaging studies clearly shows that during placebo treatments higher-order cortical regions have a modulatory role in coordinating subcortical regions of the brain that process pain responses (reviewed by Wager and Atlas[16]), all of which reinforce the importance of emotion and cognition, particularly expectancy, in potentiating (or reducing) analgesic responses to medication.

Treatment in therapeutic areas other than pain and depression are surely influenced by the nature of the interactions between patient and clinician to varying degrees. A recent meta-analysis revealed that attempts to improve the patient-clinician relationship improved health outcomes in a variety of disease states by a small but significant degree.[17] The meta-analysis included 13 studies in which an objective outcome (eg, weight loss, smoking cessation, lowering blood pressure or hemoglobin A1c) or validated subjective outcome (eg, improved health-related quality of life, reduction in pain, depression, and/or anxiety) was compared between patients treated by health care providers who either did or did not employ a systematic manipulation of the patient-clinician interaction (eg, better communication skills, more empathy, not interrupting, better eye contact, etc). The authors specifically did not include studies that measured only intermediate outcomes, such as compliance with treatment or patient satisfaction. Across the studies, the authors found that the interventions improved outcomes to a modest but significant degree, noting that the effect size was comparable to those resulting from such interventions as using aspirin to prevent myocardial

infarction over five years and smoking cessation to prevent male mortality over eight years.[17] Because the few studies that qualified for the meta-analysis included a majority in which manipulation of the clinician-patient interaction was not the primary intervention and which also studied other interventions directed at patient behavior, etc, further research that directly and specifically targets the patient-clinician relationship may show larger effects.

Colloca and Barsky have summarized the neurobiology of placebo and nocebo responses and described some of the clinical implications of their occurrence.[18] While more research is needed specifically targeted at discovering what qualities of the clinician-patient interaction most improves health outcomes, some basic principles for pharmacists can be suggested based on the foregoing observations for pain and depression. The expectation of relief by the patient can be supported by specifically describing and emphasizing the established benefits of a drug, while nocebo responses could be minimized by not overly elaborating the possible adverse events reported for a drug and stressing the rarity of such events. An attentive and caring demeanor on the part of a pharmacist when interacting with a patient may trigger the same mechanisms that occur in placebo responses and should help relieve anxiety and any negative expectations that patients often carry when dealing with a medical disorder and interacting with the health care system. In general, promoting a positive attitude in a patient when discussing a medication may help activate their normal internal healing mechanisms. The question for pharmacists and researchers is how to do this in practice.

Many calls for patient-centered, empathetic, and humanistic care have appeared in journals from a variety of disciplines, including this one.[19,20] These are typically based on moral and ethical grounds, but the results of the placebo studies described here strongly suggest that the attitudes and communication styles consistent with empathetic medical care can have a measurable positive impact on clinical outcomes. Furthermore, when judging the quality of a health care provider, patients value such interpersonal skills ("bedside manner") more than other factors such as their own health outcomes, the accuracy of diagnosis, or the training and education that the health care provider received.[21] The Academy can and should research the psychosocial aspects of performing the job of a pharmacist and train their students in evidence-based techniques that improve outcomes. In addition to this long-term goal, the Academy can easily and quickly promote awareness in student pharmacists of the impact of psychosocial variables on health outcomes by making some minor adjustments to the current curricula. When topics concerning ethics, professionalism, and "bedside manner" are taught, the known biological sequelae of psychosocial variables should be described. Conversely, when the biology and pathophysiology of disease states are taught, the mechanisms of placebo responses and the biological impacts of other psychosocial manipulations should be included, especially for the important therapeutic areas of pain and major depression. Educators can hope that when students learn the biological bases for placebo and other related healing responses, they will be more inclined to actually learn and practice the psychosocial skills necessary to promote them. While such procedural and interpersonal skills can be explicitly described and taught in didactic coursework, it may be that they are best learned through modeling by and feedback from clinical mentors and preceptors while students are completing their intermediate or advance pharmacy practice experiences. No matter how this content is presented, pharmacy educators must be aware of the need for it and then consciously and deliberately enact the principles of empathetic, patient-centered care in their own practice for students to witness.

The Accreditation Council for Pharmacy Education requires Doctor of Pharmacy programs to ensure that their graduates are "able to examine and reflect on personal knowledge, skills, abilities, beliefs, biases, motivation, and emotions that could enhance or limit personal and professional growth" (Standard 4.1. Self-awareness) and that they "exhibit behaviors and values that are consistent with the trust given to the profession by patients, other health care providers, and society" (Standard 4.4. Professionalism). Many of the skills that must be developed to achieve these professional standards are outside of the cognitive, knowledge-based domain of Bloom's Taxonomy of Educational Objectives and fall into the affective, emotion-based domain of the taxonomy. It seems self-evident that self-awareness and professionalism are worthy goals in themselves for pharmacists in order to maintain good work environments and respect for the profession. However, the evidence described here suggests that competence in such "soft skills" could measurably improve health outcomes in some very common disease states, and has revealed some of the psychological and physiological mechanisms by which these aspects of patient care can affect outcomes. Thus, there are physiological bases for why Doctor of Pharmacy students should consciously learn (and programs should deliberately teach) such skills in the affective domain to help promote optimal health outcomes. There is an old adage in medicine that states, "the best way to care for a patient is to care about them." The pharmacy profession has an ethical duty to research, teach, and enact practices that promote such caring.

ACKNOWLEDGMENTS

The author thanks Clipper Young, PharmD, and Kelan Thomas, PharmD, for helpful discussions.

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